REMARKS

Objections and Rejections and Rejections Withdrawn

The Examiner has withdrawn the following objections and rejections:

(I) The objection to the title is withdrawn.

(II) The objection to claim 2 for reciting non-elected sequences is withdrawn.

(III) The rejection of claims 1-6 under 35 U.S.C. 101 for lack of a specific and substantial utility. Specifically, the Examiner stated the specification supports a specific and substantial utility for the cDNA of SEQ ID NO:2 in the diagnosis of uterus tumor liomyoma.

Priority

The Examiner maintains that the instant application is not entitled to the priority date of USSN 09/325,993 and 08/948,197, because the parent applications do not meet the requirements under 35 U.S.C. 112, first paragraph. Specifically, the Examiner stated, while the parent applications disclose the claimed nucleic acid sequence and the encoded polypeptide, neither of the parent applications provide a specific and substantial asserted utility or a well established utility for the claimed invention. The Examiner stated that neither of the parent applications disclose the expression of SEQ ID NO:2 in cancerous tissues and not in normal tissues as taught in Example VIII of the instant application. Accordingly, instant claims 1-6 are accorded the filing date of the instant application, which is 29 May 2001.

Applicants Response

Applicants disagree that both well established utilities, as well as specific and substantial asserted utilities for the claimed invention are not disclosed in the parent application, USSN 08/948,197 that are fully enabled by the prior application and therefore that the claimed invention, as recited in at least claims 1-6 of the instant application, clearly meets the requirements under 35 U.S.C. 112, first paragraph, and should properly be accorded the filing date of the parent application of 9 October 1997.

Applicants have previously summarized the applicable legal standard for utility in the response filed June 25, 2003. Despite the uncontradicted evidence that the claimed polypeptide

is a member of molecular co-chaperone family of proteins, related specifically to p23, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the family toPR23P. In the instant Office Action, the Patent Examiner takes the position that unless Appellants can identify which particular biological function within the class of molecular co-chaperones is possessed by PR23P, utility cannot be imputed. To demonstrate utility by membership in the class of p23 related molecular co-chaperones, the Examiner would require that all family members possess a "common" utility. See Final Office Action, page 9.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[1]

The Examiner addresses PR23P as if the general class in which it is included is not the molecular co-chaperone family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the molecular co-chaperone family does not. The molecular co-chaperone family is sufficiently specific to rule out any reasonable possibility that PR23P would not also be useful like the other members of the family.

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[1]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

Because the Examiner has not presented any evidence that the molecular co-chaperone class of proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the PR23P encoded by the claimed polypeptide is useful.

Secondly, applicants also reiterate that the asserted use the claimed invention in the diagnosis, treatment, and evaluation of therapies for treatment of cancer, is fully supported by the parent application, specifically for the reasons stated in the previous response to Office Action, at page 11, last paragraph through page 12, second paragraph.

Finally, the Examiner has completely ignored a well established utility for the claimed polynucleotides in toxicology testing and drug discovery that was well established prior to the 1997 filing date of the parent application USSN 08/948,197. Since the Examiner has refused to address this well-established utility for the claimed invention specifically discussed by applicant at page 12 in the previous response, applicants reiterate this utility supported by a declaration under 37 CFR 1.132 of Dr. John C Rockett. The Rockett declaration describes, in particular, how the claimed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing toxicological profiles for potential toxicants. Dr. Rockett states, for example, in ¶ 15, bottom of page 8 of the declaration that, with reference to well-characterized toxicants:

> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by such toxicants, this would appear a longer term goal, as the majority of human genes have not been sequenced, far less their functionality determined. However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard ... (original emphasis).

Thus, the use of the claimed polynucleotides in gene expression profiling for potential toxicants represents a well established use independent of any functionality for the encoded polypeptide or known mechanism of toxicity for the encoded polypeptide.

The fact that the Rockett Declaration is being submitted in response to the Examiners' failure in the Final Office Action to address applicants own testimony related to the well established utility of the claimed invention in toxicology testing constitutes, by itself, "good and

sufficient reasons" under 37 C.F.R. § 1.195 why that Declaration was not earlier submitted and should be admitted at this time.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1 and 3-6

The Examiner has rejected claims 1 and 3-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claim 1 of the instant application is drawn, in part, to a nucleic acid encoding variants of SEQ ID NO:1 having at least 95% amino acid identity to SEQ ID NO:1. However, the Examiner stated, the written description in this case is only commensurate to an isolated nucleic acid encoding the polypeptide of SEQ ID NO:1, and therefore is not commensurate in scope with the claims. The Examiner stated that "the court" (no specific reference given) held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. Adequate written description requires more than a mere statement that is is part of the invention. The Examiner stated that the court indicated that the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. However, the Examiner stated, no disclosure beyond the mere mention of variants is made in the specification. This is insufficient to support the generic claims a provided by the Interim Written Description Guidelines published 21 December 1999.

Applicants Response

Applicants disagree that the claimed "variants" of the polynucleotides encoding PR23P lack adequate written description in accordance with 35 U.S.C. § 112, first paragraph and the Written Description Guidelines.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., **complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.** If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (Emphasis added)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:2 are specifically disclosed in the priority application, USSN 08/948,197 (see, for example, page 3, lines 5-7 and lines 14-15). Variants of SEQ ID NO:1 are described, for example, at page 3, lines 10-13. In particular, the preferred, more preferred, and most preferred variants (80%, 90%, and 95% amino acid sequence similarity to SEQ ID NO:1) are described, for example, at page 14, lines14-18. Incyte clones in which the nucleic acids encoding the human PR23P were first identified and libraries from which those clones were isolated are described, for example, at page 13, lines 24-29 of USSN 08/948,197. Chemical and structural features of PR23P are described, for example, on page 14, lines 1-9. Given SEQ ID NO:1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 having at least 95% sequence identity to SEQ ID NO:1. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The Office Action has further asserted that the claims are not supported by an adequate written description because

> Claims 1 and 3-6 contain "subject matter which is not described in the specification in such a was as to reasonably convey to one skilled in the relevant

> art that the inventor(s), at the time the application was filed, had possession of the claimed invention".
>
> page 4 of the Final Office Action

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind to the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

> 1. An isolated cDNA comprising a nucleic acid sequence encoding a protein having an amino acid sequence of:... a naturally-occurring variant of the amino acid sequence of SEQ ID NO:1 having at least 95% amino acid sequence identity to the amino acid sequence of SEQ ID NO:1...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides or polypeptides. The polynucleotides or polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis

of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to co-chaperone proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as co-chaperone proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 156 amino acid residues). This variation is far less than that of all potential co-chaperone proteins related to SEQ ID NO:1, i.e., those co-chaperone proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written

description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of October 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 or SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1 and 3-6

The Examiner has rejected claims 1 and 3-6 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid consisting of SEQ ID NO:2 and the complete complement thereof, does not reasonably provide enablement for an isolated nucleic acid encoding the polypeptide of SEQ ID NO:1 or which encodes variants of SEQ ID NO:1 having 95% sequence identity to SEQ ID NO:1.

The Examiner stated that while the nucleic acid of SEQ ID NO:2 can be used to diagnose uteus leiomyoma, it cannot be used to diagnose squamous cell carcinoma of the lung; firstly, because it is unclear from Example VIII as to the nature of the lung tissues used in the studies, and secondly, because the specification discloses the expression of the nucleic acid in only one squamous cell carcinoma library compared to three normal libraries and, the Examiner stated, this is not statistically significant. The Examiner also again denied that the specification sufficiently characterizes the protein encoded by SEQ ID NO:2 as a molecular co-chaperone or as having a common utility with a molecular co-chaperone.

The Examiner stated that applicants have not shown that any other nucleic acid or variant, even degenerate variants encoding the same protein as SEQ ID NO:2, was expressed in uterus leiomyoma. The Examiner further stated that gene expression is not necessarily correlated with protein expression citing a single reference of Pennica et al. and concluding therefore, that protein levels cannot be accurately predicted from the level of expression of the corresponding gene.

Applicants Response

Applicants first of all disagree that SEQ ID NO:1 is not adequately characterized as a molecular co-chaperone protein related to p23 for the reasons given above in response to the rejection of claims under 35 U.S.C. § 101. However, regardless of the biological function of SEQ ID NO:1, the uses of the polynucleotides of the invention, including variants of SEQ NO:2 and of other polynucleotides encoding SEQ ID NO:1, are described and enabled throughout the specification, e.g., as hybridization probes (see pages 12-13); for the diagnosis of disease conditions (see page 17); for chromosomal mapping (see pages 29-30); and in microarray assays to monitor gene expression patterns (see page 13). None of the described uses of the polynucleotides require a functional association of an encoded polypeptide. In particular, the use of variants of the polynucleotide encoding SEQ ID NO:1 "in hybridization, amplification, and screening technologies to identify and distinguish among SEQ ID NO:2 and related molecules in a sample" (page 10, lines 30-31) does not depend on whether or not such variants might be functional or non-functional. Thus variants of the polynucleotides encoding SEQ ID NO:1 are fully enabled by the specification.

The Examiner also cites a single reference (Pennica et al.) with respect to a general allegation that levels of protein expression cannot be accurately predicted from the level of

expression of the corresponding gene, and therefore that levels of SEQ ID NO:1 expression in the instant would not be predictable from levels of expression of the corresponding mRNA as represented by SEQ ID NO:2. Applicants first of all note that the cited reference discloses a lack of correspondence between levels of "amplified DNA" expression and levels of mRNA expression. Levels of corresponding protein expression are not addressed.

In addition, however, Applicants point out that it is widely recognized that regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification and protein turnover. While steady state mRNA levels are not always directly proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publication have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. According to B. Lewin [(1997) Genes VI Oxford University Press, Inc. New York, NY] (pages attached):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to study in the *in vitro* systems... ***For most genes, this is a major control point; probably it is the most common level of regulation.*** [page 847, emphasis added].

> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that ***the overwhelming majority of regulatory events occur at the initiation o transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation.*** [pages 847-848, emphasis added]

Thus, the Examiner provides no convincing evidence that this well established principle, that levels of expression of an mRNA are *generally* recognized as reflecting corresponding levels of protein expression, would be doubted by the skilled artisan and, in particular, that levels of the protein of SEQ ID NO:1 did not likely correspond with those of its encoding polynucleotide, including SEQ ID NO:2. Thus there is a substantial likelihood that all polynucleotides encoding SEQ ID NO:1 would be similarly useful in, for example, the detection and diagnosis of uterine cancer.

For all of the above reasons, applicants submit that the polynucleotides of the invention, including degenerate variants of the polynucleotide encoding SEQ ID NO:1, as well as polynucleotides encoding variants of SEQ ID NO:1having at least sequence 95% identity to SEQ ID NO:1, are fully enabled by the specification, and therefore request withdrawal of the rejection of claims 1 and 3-6 under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 102(b), Rejection of Claims 1-6

The Examiner has maintained the rejection of claims 1-6 under 35 U.S.C. § 102(b) as anticipated by Yue et al. (1999) for the reasons of record given in Paper No.12. Specifically, the Examiner reiterated the reasons given for denying the claimed invention as recited in claims 1-6 the filing date of the parent applications cited by applicant. Therefore Yue et al. anticipate the claimed invention.

Applicants Response

Applicants reiterate that, for the reasons previously given in response to the rejection under 35 U.S.C. § 101 filed 6/25/2003, specifically at pages 10-12 of that response, as well as those given above in the current response with respect to the "Priority" objection made by the Examiner, that both well established utilities, as well as specific and substantial asserted utilities for the claimed invention are disclosed in the parent application, USSN 08/948,197 that are fully enabled by the prior application. Therefore, the claimed invention, at least as recited in at least claims 1-6 of the instant application, clearly meets the requirements under 35 U.S.C. 112, first paragraph and should properly be accorded the filing date of the parent application of 9 October 1997. Therefore, Yue et al do not anticipate the claimed invention, at least as recited in claims 1-6, and withdrawal of the rejection under 35 U.S.C. 102(b) is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited. Applicants further request that, upon allowance of claim 1, claims 7-12 be rejoined and examined as methods of use of the compositions of matter of claim 1 that depend from and are of the same scope as claim 1 in accordance with *In re Ochiai* and the MPEP § 821.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

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Attachment(s): Brenner et al. Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078
B. Lewin Genes VI Oxford University Press, Inc. New York, NY (1997) 847-848
Declaration of John C. Rockett, Ph.D., under 37 CFR § 1.132, with Exhibits A-Q